The corticotropin-releasing factor family in the urogenital system (Review)

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Abstract. Corticotropin-releasing factor (CRF) is acknowledged for its role in stress responses and hormonal regulation, and it has been identified as a critical factor in the urinary and reproductive systems. CRF is integral to key processes, such as waste elimination, fluid balance, reproductive function and hormonal activity. Notably, dysregulation of CRF signaling is linked to conditions such as urinary incontinence, chronic bladder pain/interstitial cystitis (IC), benign prostate hyperplasia and cancer. CRF interacts with related molecules, including urocortins (UCNs), CRF receptors (CRFR1 and CRFR2) and CRF binding protein, to influence inflammation, muscle contractions and cancer progression. Furthermore, CRF influences hormone production and sperm development in the testes by affecting Leydig and Sertoli cells. UCN1 and CRFR2 in the prostate are associated with inflammatory responses and the advancement of prostate cancer. In the bladder, CRF modulates urination, with dysfunction linked to an overactive bladder, chronic pain and malignancy. Furthermore, CRF signaling in the kidneys facilitates normal function while potentially playing a role in the development of kidney cancer. These findings highlight the dual function of CRF as a regulator of health and a potential contributor to disease. Comprehending these mechanisms may facilitate the development of innovative therapies for conditions such as IC or prostate disorders, which currently have no effective treatments. The present review promotes further investigation into the various functions of CRF, with the objective of translating findings into novel strategies that enhance patient quality of life.

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1. Introduction

Corticotropin-releasing factor (CRF), a peptide produced in the hypothalamus, is primarily recognized for its role in regulating the body's stress response. This occurs through the activation of the hypothalamic-pituitary-adrenal axis, an essential hormonal pathway. CRF specifically stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH), which subsequently triggers cortisol production from the adrenal glands, thereby preparing the body to manage stressors (1,2). However, besides of their well-documented central functions, CRF and its family members-(UCNs 1, 2, 3), two receptor types (CRFR1 and CRFR2) and CRF binding protein (CRFBP)-express important roles both in the central nervous system and many peripheral organs, including the urogenital system (3,4). For instance, CRF and its relatives influence cardiovascular health. Exogenous CRF increases blood pressure in rats. Conversely, CRFR2 knockout mice develop hypertension, while UCN1 counteracts this effect (5,6). Similarly, UCN2 and UCN3 enhance heart muscle contractions, though their long-term effects on heart function remain complex (7,8). In addition to their role in the cardiovascular system, these molecules also influence digestion: UCNs prolong gastric emptying whereas CRF inhibits the release of stomach acid (9,10). CRF receptors regulate gut motility and inflammation, as evidenced in inflammatory bowel diseases such as Crohn's and ulcerative colitis, where levels of UCN1 and UCN2 increase (11,12). In reproduction, CRF and UCNs are dynamically active during the menstrual cycle and pregnancy (3). Further, CRF may serve as a biomarker for preterm

labor prediction, and their role in vasodilation is relevant in conditions such as pre-eclampsia (13,14). It additionally facilitates uterine contractions, functioning in conjunction with oxytocin during parturition (15,16). CRF takes part in the immune response and in the modulation of inflammation, since it is expressed in the thymus, spleen, lymphocytes and mast cells (3,17,18). For example, UCN1 induces cytokine release, whereas CRF functions as a pro-inflammatory signal (3,19,20). It participates in the activity of mast cells and vascular permeability within the lung (Fig. 1) (21).

Recent studies highlight CRF family members in human urogenital tissues, where they regulate inflammation, muscle activity, and even cancer progression (4,22). Despite increasing interest, the roles of these entities within the system are not well understood. This review attempts to present some synthesized knowledge on CRF, UCNs, and their receptors within the urinary and reproductive systems. The distribution and mechanisms of action and their dual roles in the promotion of health and the pathogenesis of diseases such as interstitial cystitis (IC), prostate cancer (PCa), and reproductive dysfunctions are discussed. Through a critical assessment of the current literature, this review investigates the promise of targeting CRF signaling pathways for the development of therapeutics in insufficiently studied urogenital disorders and improving patient outcomes.

2. Review methods

A thorough search and review was performed utilizing the search terms '(CRF* OR UCN* OR CRH* OR Urocortin) AND (Prostate OR Renal OR Kidney OR Bladder OR Testes OR Testis OR Urogenital)'. An extensive electronic search was conducted using the MEDLINE database. The literature search was completed by November 1, 2024. The study's search strategy was implemented without restrictions on publication year. We additionally examined the references cited in the included studies.

3. CRF and testes

Following the discovery and characterization of CRF, Bardin *et al* (23) identified the presence of ACTH and Pro-opiomelanocortin in the testes of experimental animals in 1984. As is known, hypothalamic CRF is associated with the release of ACTH and Pro-opiomelanocortin from the pituitary gland (1,2). The logical next step was to investigate the presence of CRF in the male reproductive system. The first literature report on this subject appeared in 1987, when researchers detected CRF mRNA in the testes of adult rats (24). A year later, new experiments in rats identified CRF in Leydig cells and the germ cells of the testes (25). Subsequently, CRF was found in the testes of other animals, suggesting that it might play a significant role in gonadal function (26). Researchers conducted targeted experiments involving androgens and Leydig cells to determine the role of CRF. The biological hypothesis of the existence of high-affinity functional receptors for CRF appears to be valid (27). In embryonic and adult cultured Leydig cells from rats, CRF inhibited human chorionic gonadotropin (hCG)-induced androgen production in a dose-dependent manner (27). However, it did not affect the basal levels of testosterone and paradoxically did not stimulate cyclic adenosine monophosphate (cAMP) production as expected based on results from other tissues (27). These data suggest that CRF receptors may not be coupled to G-proteins, potentially exerting negative feedback on hCG stimulation of Leydig cells. Other researchers with different study designs confirmed these findings. In rat Leydig cells, hCG induced a dose-dependent increase in CRF secretion (28). In the testis, CRF is involved in the autocrine signaling of Leydig cell function, exerting a negative action. Another possible mechanism of CRF's 'anti-reproductive' action is related to β-endorphin. CRF appears to promote its secretion, which in turn inhibits the action of follicle-stimulating hormone on Sertoli cells (29). Luteinizing hormone (LH) initiates this pathway, releasing serotonin and activating 5-HT2 receptors to produce CRF (29). This pathway garners significant clinical interest, since an increase in serotonin may exacerbate testicular dysfunction via CRF in certain pathological situations affecting the micro-testicular environment, such as varicocele or inflammation/infection. It is worth noting here that CRF also has an inhibitory function at the central level, affecting sexual behavior and LH secretion (29).

The results of a later study were partially conflicting, showing that CRF administration with or without hCG increased cAMP and steroid levels. That study also used the MA-10 rat Leydig cell cancer line, which responded better to CRF treatment (30). Another study reported similar findings, demonstrating increased intracellular cAMP and testosterone following CRF administration (31). However, these experiments involved mice, not rats. The same research team did not observe changes in cAMP and steroids after CRF administration in rats, which is consistent with previous studies. A new finding was the discovery of CRFR1 mRNA in mouse Leydig cells (31). The actions of CRF in steroidogenesis seem to occur through the activation of CRFR1. For over 25 years after the discovery of CRF, there was no research on sperm or UCNs. In 2007, Tao *et al* (32) reported the inaugural identification of mRNA and peptides UCN1, CRFR1, and CRFR2 in mature spermatozoa, spermatocytes, and spermatogonia, respectively. Regarding the functional role of UCN1, there were two main findings related to male reproductive functions. First, it reduced the acrosome reaction, and second, it reduced sperm motility (32). At the cellular level, it decreased sperm intracellular Ca^{2+} (32). This observation partly explains both effects, as intracellular Ca^{2+} plays an essential role in sperm motility and the acrosome reaction (32). The design of the above studies and the presence of conflicting results make the landscape quite unclear.

Moreover, it was infeasible to extrapolate the results of studies where the administration of a CRF antagonist failed to mitigate the effects of CRF. However, as Rivier (33) notes, many of the observed effects of CRF were actually due to UCN1. In her experiments, she observed that UCN1 and the selective CRFR1 agonist, Stressin1, reduced the testosterone response to hCG in rats. UCN2 and UCN3, which are selective for CRFR2, did not exhibit the same phenomenon. The strength of the results increased as the effects appeared regardless of the route of UCN1 administration (intracellular or intravenous), and there was a reversal of its action with the use of astressin B, a mixed CRFR1,2 antagonist One issue

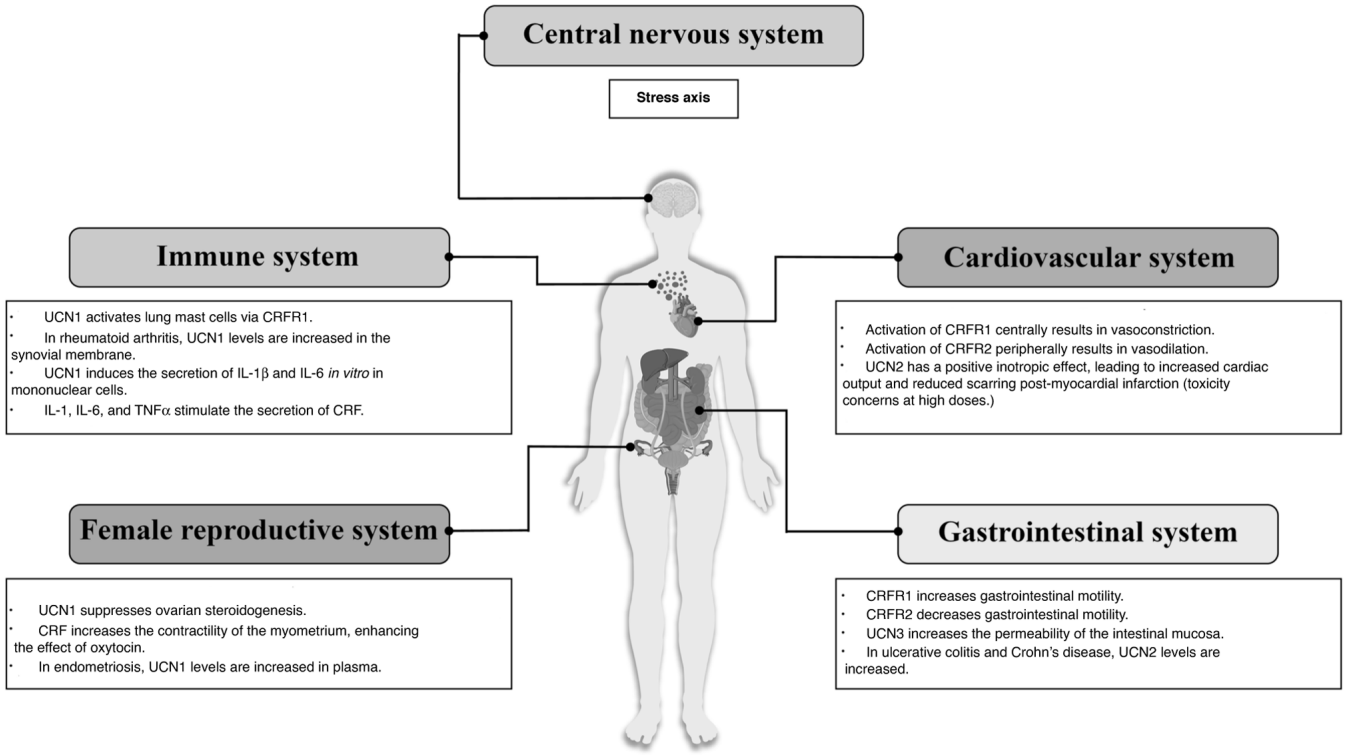

Figure 1. Graphical representation of the involvement of the CRF system in the different target organs. CRF, corticotropin-releasing factor; CRFR1, corticotropin-releasing factor receptor 1; CRFR2, corticotropin-releasing factor receptor 2; IL-1β, interleukin-1β; IL-6, interleukin-6; TNFα, tumor necrosis factor α; UCN1, urocortin 1; UCN2, urocortin 2; UCN3, urocortin 3.

that arose with the study was that CRF antagonists did not reverse the inhibitory effect of alcohol on testosterone release via hCG. This observation raises concerns, as it is known that alcohol enhances UCN1 gene expression.

Rivier's objections were confirmed in a subsequent study showing that CRF mRNA expression in the testes was negligible compared to that in the hypothalamus (34). The experiments were conducted in rats and showed strong UCN1 mRNA expression with weaker UCN2,3 expression (34). Immunohistochemistry demonstrated that UCN1 expression was exclusively in Leydig cells. Contrary to Rivier's experiments, alcohol administration in rats significantly increased UCN1 mRNA levels without affecting the expression of UCN2, UCN3, CRF, CRFR1, or CRFR2 (34).

Finally, the most recent research on the CRF family's presence and function in the testes used cell lines and tissue preparations from rats and mice (35). This study focused on embryonic testes, aiming to investigate a crucial chapter of biology: the reproductive development of the male embryo. The study concluded that CRF and CRFR1 activation stimulates steroidogenesis in embryonic Leydig cells. Researchers detected these results in both mice and rats, either *in vivo* or *ex vivo* (35). Table I summarizes the aforementioned studies on CRF and testes

4. CRF and prostate

The first report regarding CRF in the prostate appeared in 1987 (36). However, the functional presence of the CRF family in the prostate was investigated for the first time in 2002 (37). Specifically, researchers utilized samples from humans following radical prostatectomy, transurethral resection of the prostate, and transrectal biopsy. In total, 19 samples were examined, of which nine had PCa. Both the peptide and mRNA of UCN1 were expressed in all tissues (37). The UCN1 peptide was found in the basal membrane, the secretory epithelium, the smooth muscle fibers of the stroma, and the lymphatic vessels using immunohistochemistry. Also, UCN1 was identified in cancer cells, indicating its potential involvement in the pathophysiology of the prostate, despite no observed differences in expression levels across the groups. The known involvement of UCN1 in inflammation, cell proliferation, and the relaxation of the smooth muscle fibers tone via CRFR2 warranted further study.

In a subsequent study examining human tissues, the expression of CRFR2 was evaluated. The presence of CRFR2 was studied in five open prostatectomy preparations and three radical cystoprostatectomy preparations (38). The results of PCR and immunohistochemistry clearly demonstrated the presence of the receptor, marking the first such finding in the literature. As previously mentioned, the activation of CRFR2 may have anti-inflammatory, anti-proliferative, and relaxing properties, making it a target for future therapies in pathological gland conditions, such as (BPH). The next step was to investigate and compare the expression of CRFR2 in PCa. In 32 patient samples following radical prostatectomy, a comparison was made between cancerous and normal sections (39). The notable observation was that CRFR2 ceased to be expressed in the areas where cancer developed. Although UCN1 is expressed in PCa, CRFR2 mRNA (PCR)

Table I. Summary of the main findings and effects of CRF family members in the testes.

First author, year	Tissue specimen or cell lines	CRF family member	Findings	Possible mechanism or relation	(Refs.)
Thompson *et al*, 1987	Testes of adult rats	CRF	Detection of CRF mRNA	Presence of CRF in the male reproductive system	(24)
Yoon *et al*, 1988	Leydig cells and germ cells of testes	CRF	Identification of CRF	Suggests a significant role in gonadal function	(25)
Audhya *et al*, 1989	Testes of various animals	CRF	Found in testes	Indicates role of CRF in gonadal function	(26)
Ulisse *et al*, 1989	Cultured Leydig cells of rats	CRF	Inhibited hCG-induced androgen production	CRF receptors may not be coupled to G-proteins, negative feedback on hCG stimulation of Leydig cells	(27)
Fabbri *et al*, 1990	Rat Leydig cells	CRF	hCG induced a dose-dependent increase in CRF secretion	CRF involved in autocrine signaling of Leydig cell function, negative action	(28)
Dufau *et al*, 1993	Sertoli cells of rats	CRF	Promoted β-endorphin secretion, inhibited FSH action	Pathway involving LH, serotonin release, and CRF production	(29)
Huang *et al*, 1995	MA-10 rat Leydig cancer cell line	CRF	Increased cAMP and steroid levels	Conflicting results with previous studies	(30)
Heinrich *et al*, 1998	Leydig cells of mice and rats	CRF, CRFR1	Increased intracellular cAMP and testosterone	CRF actions in steroidogenesis via CRFR1	(31)
Tao *et al*, 2007	Mature spermatozoa, spermatocytes, spermatogonia	UCN1, CRFR1, CRFR2	Reduced acrosome reaction, decreased sperm motility	Decreased sperm intracellular Ca^{2+}	(32)
Rivier, 2008	Rats	UCN1, CRFR1, CRFR2	Reduced testosterone response to hCG	UCN1 and selective CRFR1 agonist reduced testosterone response	(33)
Lee *et al*, 2011	Rats	UCN1, CRFR1, CRFR2	Increased UCN1 mRNA levels with alcohol administration	Alcohol increased UCN1 without affecting other CRF family members	(34)
McDowell *et al*, 2012	Embryonic testes of rats and mice	CRF, CRFR1	Stimulated steroidogenesis	CRF and CRFR1 activation in embryonic Leydig cells	(35)

CRF, corticotropin-releasing factor; UCN1, urocortin 1; CRFR1, corticotropin-releasing factor receptor 1; CRFR2, corticotropin-releasing factor receptor 2; FSH, follicle-stimulating hormone; LH, luteinizing hormone; hCG, human chorionic gonadotropin; cAMP, cyclic adenosine monophosphate.

and its peptide (immunohistochemistry) were absent. It is unknown whether this is the cause or result of PCa and disease progression, as CRFR2 activation appears to inhibit angiogenesis (39). To further clarify the role of the CRF family in PCa, Jin *et al* (40) studied the presence and involvement of CRFR1 and CRFR2 in human and rat PCa cell lines. The expression of both receptors was initially identified in both cell lines (rat RM-1, human LNCaP). A significant observation from the experiments was that UCN2 favored cell proliferation, while CRF promoted apoptosis. Conclusions were drawn after checking the expression of typical peptides for cell proliferation and apoptosis, Bcl-2 and Bax, respectively. UCN2 increased the expression of Bcl-2 and decreased the expression of Bax, whereas CRF had the opposite effect (40). The use of specific antagonists for CRFR1 and CRFR2, antalarmin and antisauvagine-30 (aSVG30), respectively, inhibited the effects of CRF and UCN2, confirming the significance and potential impact of the findings.

Moreover, the CRF family's potential involvement in the pathophysiology of PCa, in addition to BPH, is an intriguing area for further research and exploration. Table II provides a summary of the aforementioned studies on CRF and prostate.

5. CRF and bladder

CRF and urinary tract function. The urothelium is the inner layer of the urinary tract and bladder, serving as a vital barrier between blood and urine. The transitional cells that make up the urothelium have properties similar to those of neurons, as they use similar ion channels and express similar receptors (41-43). Initially, research regarding CRF and the bladder focused on the mechanism and physiology of urination. In 1984, Vincent and Satoh (44) found a group of neurons in the brainstem that were reactive with the CRF peptide (or CRF-like). This group of neurons was found in the same place as the pontine micturition center in rats, which suggests that CRF is involved in controlling urination. Later, it was confirmed that this region of the pons in the brainstem is the Barrington nucleus, which contains neurons rich in CRF (45). The Barrington nucleus is considered the pontine-spinal micturition center, functioning as an on-off switch. Early functional experiments in rats showed that CRF can inhibit urination (46). Stimulation of the Barrington nucleus by glutamate injection causes bladder contraction. Researchers observed that bladder contractions increased after intrathecal administration of a CRF antagonist (D-PheCRH12-41), whereas after CRF administration, they decreased (46). These observations suggest that CRF may be involved in the urinary continence mechanism. Although the Barrington nucleus acts as a switch for initiating and ceasing urination, CRF is not exclusively involved in either function.

Contrary to the aforementioned findings, which involved anesthetized rats, were the results of a study with alert experimental animals (47). Intraperitoneal and intrathecal CRF injections reduced the interval between detrusor contractions by 26 and 28%, respectively. Additionally, the intrathecal injection reduced the volume of urination by 34.7%, while the intraperitoneal injection reduced it by 30.2% (47).

The administration of the non-selective CRFR antagonist, astressin, inhibited these effects, indicating the involvement

Table II. Summary of the main findings and effects of CRF family members in the prostate.

First author, year	Tissue specimen or cell lines	CRF family member	Findings	Possible mechanism or relation	(Refs.)
Asa *et al*, 1987	Human prostate tissue	CRF	First report of CRF presence	Initial identification	(36)
Arcuri *et al*, 2002	Human prostate tissue	UCN1	Expression in various tissues, including cancer cells	Potential involvement in prostate pathophysiology	(37)
Tezval *et al*, 2008	Human prostate tissue	CRFR2	Demonstrated presence in prostate	CRFR2 may have anti-inflammatory, anti-proliferative, and relaxing properties	(38)
Tezval *et al*, 2009	Prostate tissue from patients	CRFR2	Absent in cancerous areas	CRFR2 activation appears to inhibit angiogenesis	(39)
Jin *et al*, 2011	Human and rat prostate cell lines	CRFR1, CRFR2	UCN2 promoted cell proliferation, CRF promoted apoptosis	Expression of Bcl-2 and Bax	(40)

CRF, corticotropin-releasing factor; UCN1, urocortin 1; CRFR1, corticotropin-releasing factor receptor 1; CRFR2, corticotropin-releasing factor receptor 2; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein.

of receptors in the urination mechanism. McFadden *et al* (48) used adenoviruses containing the cDNA of CRF to investigate novel genetic therapies utilizing gene transfer vehicles. The use of viral vehicles in the model of male rats resulted in increased expression of CRF in the Barrington nucleus. The overexpression of this gene is associated with increased residual urine and decreased flow pressure, indicating that CRF impedes the urination process (48). Analogous to the stress model, rats subjected to genetic modification did not exhibit the same urodynamic profile. This is partly explained by the fact that the expression of CRF in the viral vehicle model was much higher than in the stress model, and compensatory mechanisms (e.g., reduced receptor expression) may have developed to preserve spinal centers. As evidenced by all studies, the effect of CRF on bladder function is unclear, whether it is direct or indirect. A recent study attempted to answer this research question by simultaneously examining CRF and muscarinic receptors of the detrusor muscle, which are known to directly influence bladder kinetics (49). Researchers used male rats exposed to a psychological stress challenge in a communication cage. The stress group exhibited higher levels of CRF mRNA expression, CRFR1, and M2,3 muscarinic receptors in the bladder compared to the normal group. Functionally, the stress group had more detrusor contractions and a smaller urination volume. These differences normalized after the use of the CRFR1 antagonist, antalarmin. CRF alone did not influence detrusor contraction; however, activation of CRFR1 in response to stress appears to mediate muscarinic contraction through M3 receptors (49).

Another recent study investigated the involvement of the CRF family in urination using a modern genetic method for controlling neuron activity called optogenetics (50). The method activated CRF neurons in the Barrington nucleus to study the urination mechanism. Optogenetic activation of CRF neurons had an inhibitory effect on voluntary urination in both male and female mice (50). Finally, regarding bladder sensitivity and pain threshold, female rats were studied after stress induction using the footshock protocol (51). The group subjected to footshock for seven days showed increased CRFR2 expression and decreased CRFR1 in the spinal cord. An increase in UCN2 and a decrease in UCN3 were noted in both the spinal cord and the bladder. The neural responses of the experimental animals were subsequently examined following bladder overdistension and the administration of antalarmin and aSVG30. The administration of aSVG30 resulted in a decrease in neural responses triggered by bladder distension in rats exposed to footshock for seven days (51). These findings indicate that CRFR2 is linked to bladder sensitivity, establishing a foundation for additional research on the application of a selective antagonist in pathological pain conditions, including IC, chronic cystic-pelvic pain, and overactive bladder (OAB). Table III highlights the discussed studies on CRF and urinary tract function.

CRF and bladder pathologies. The literature has shown the relationship between stress and mood disorders, such as depression, with OAB and IC (52,53). Additionally, it is known that CRF increases during periods of anxiety and depression (52). Higher levels of anxiety exacerbate symptoms in patients with IC, as they experience more significant pain and intense urgency to urinate (53). Thus, it is hypothesized that CRF is involved in the pathophysiology of OAB and IC. Despite several studies investigating CRF's involvement in bladder function, its presence in this context remains unclear. A CRF family member was first identified in 2002 when CRFR1 overexpression was observed in mouse models with DNP4-ovalbumin-induced cystitis (54). Later, experiments in female mice with cyclophosphamide-induced cystitis showed overexpression of CRF and CRFR2 in the bladder and urothelium without identifying CRFR1 presence (55). Knowing that stress exacerbates inflammation, Boucher *et al* (56) attempted to investigate cystitis's pathophysiology concerning the wall's vascular permeability and the release of the vascular endothelial growth factor (VEGF). The study found that stress increases bladder permeability and promotes VEGF release via CRFR2, indicating its involvement in cystitis (56). A significant study investigated the expression and functional differences of the CRF system between normal and pathological urothelium in cats with IC (57). Researchers identified the expression of CRFR1 and CRFR2 in both normal and pathological urothelium using western blot analysis. CRFR2 peptide expression was significantly higher than that of CRFR1. Additionally, after culturing urothelial cells, ELISA revealed the expression of CRF and UCN1 (57). The protein expression of CRF family members did not differ between normal and pathological urothelium. However, some functional differences were observed. In normal urothelium, increased ATP release was noted following CRF administration, although this was not statistically significant. Conversely, in pathological urothelium, ATP release after UCN3 administration was statistically significant. Also, CRF and UCN3 caused exocytosis of similar-sized vesicles in normal urothelium. In contrast, in pathological urothelium, CRF-induced exocytosis was significantly greater compared to UCN3 (57). These functional differences suggest the involvement of CRFRs in the pathophysiology of IC, regardless of their quantitative expression.

Recently, researchers conducted the first study involving human material, investigating the presence and expression of CRFRs in both normal and pathological urothelium (4). Patients were divided into two groups. One included those with IC, and the other included those with IC and Hunner's ulcers who underwent bladder biopsy. Additionally, there were controls with normal urothelium reporting urinary incontinence. Immunohistochemistry demonstrated the presence of both receptors in the human bladder. CRFR1 predominantly localized in the submucosa, whereas CRFR2 was primarily located in urothelial cells. CRFR1 expression was significantly higher, while CRFR2 expression was notably lower in patients with inflammation compared to those with only incontinence. A characteristic finding was the further overexpression and underexpression of CRFR1 and CRFR2 in the group with Hunner's ulcers.

Finally, another study investigated the presence of CRF family mRNA in the human bladder (22). The results indicated a downregulation of UCN1 in bladder cancer, raising questions about its potential association with the treatment, diagnosis, or prognosis of the disease (22). Table III highlights the discussed studies on CRF and bladder pathologies.

Table III. Summary of the main findings and effects of CRF family members in bladder function and diseases.

A, Bladder function

First author, year	Tissue specimen or cell lines	CRF family member	Findings	Possible mechanism or relation	(Refs.)
Vincent and Satoh, 1984	Brainstem of rats	CRF	Identified CRF-immunoreactive neurons	Suggests CRF involvement in urination regulation	(44)
Pavcovich and Valentino, 1995	Barrington nucleus of rats	CRF	Inhibited urination	Role of CRF in urinary continence mechanism	(46)
Klausner *et al*, 2005	Rats	CRF	Reduced interval between detrusor contractions and urination volume	Involvement of CRFRs in urination mechanism	(47)
McFadden *et al*, 2012	Barrington nucleus of male rats	CRF	Increased residual urine, reduced flow pressure	Highlighted inhibitory effect of CRF on urination	(48)
Seki *et al*, 2019	Bladder of male rats	CRF, CRFR1	Increased detrusor contractions, smaller urination volume	CRFR1 activation mediates muscarinic contraction via M3	(49)
Van Batavia *et al*, 2021	Barrington nucleus of mice	CRF	Inhibited voluntary urination	Optogenetic activation of CRF neurons	(50)
Robbins *et al*, 2023	Spinal cord and bladder of female rats	UCN2, UCN3, CRFR1, CRFR2	Increased CRFR2, decreased CRFR1 in stressed rats	CRFR2 associated with bladder sensitivity	(51)

B, Bladder diseases

First author, year	Tissue specimen or cell lines	CRF family member	Findings	Possible mechanism or relation	(Refs.)
Vincent and Satoh, 1984	Mouse models with DNP4-ovalbumin-induced cystitis	CRFR1	Overexpression in cystitis	Indicated involvement in cystitis	(44)
LaBerge *et al*, 2006	Female mice with cyclophosphamide-induced cystitis	CRF, CRFR2	Overexpression in bladder and urothelium	Stress exacerbates inflammation via CRFR2	(55)
Boucher *et al*, 2010	Bladder of stressed animals	CRFR2	Increased bladder permeability and VEGF release	Indicating involvement in cystitis	(56)
Hanna-Mitchell *et al*, 2014	Urothelium of cats	CRFR1, CRFR2	Functional differences in ATP release and exocytosis	Suggests involvement in IC pathophysiology	(57)
Jhang *et al*, 2019	Human bladder biopsy samples	CRFR1, CRFR2	Overexpression in IC and Hunner's ulcers	Differences in receptor expression in pathological conditions	(4)
Mavridis *et al*, 2024	Human bladder cancer tissue	UCN1	Downregulation in bladder cancer	Potential association with treatment, diagnosis, or prognosis	(22)

CRF, corticotropin-releasing factor; CRFR1, corticotropin-releasing factor receptor 1; CRFR2, corticotropin-releasing factor receptor 2; UCN1, urocortin 1; UCN2, urocortin 2; UCN3, urocortin 3; VEGF, vascular endothelial growth factor; IC, interstitial cystitis.

6. CRF and kidney

The first report on the presence of a member of the CRF family in the kidneys was made in 1999 (58). Since then, there have been very few publications that have yet to be of significant clinical interest. The first publication, involving male rats, identified UCN1 mRNA in the kidney at low levels without providing further information (58). The subsequent publication examined the presence of UCN2 in various tissues of male mice and the changes in its expression following the administration of cortisone (59). The researchers reported a weak expression of UCN2 mRNA in the kidneys, but did not verify whether this expression changed after corticosteroid administration (59). In contrast to experiments in mice, Yamauchi *et al* (60) observed no expression of UCN2 in rat kidneys after RT-PCR analyses. The first study on CRF in humans took place in 2004 (61). Immunohistochemistry tests on autopsy materials revealed the presence of UCN3 in the kidney, particularly in the distal tubules, and confirmed the presence of UCN3 mRNA (61). The study's most important finding was that UCN3 levels were about the same in the brain and the kidneys. This suggests that UCN3 may play an autocrine or paracrine role.

Researchers have also studied the CRF system in cases of renal neoplasms. The first published study examined nephrectomy samples from patients with clear cell renal carcinoma (ccRCC) (62). The innovative finding was that UCN1 and CRFR2 mRNAs were present in both healthy and cancerous samples, with no discernible differences. Immunofluorescence demonstrated a significant observation regarding ccRCC: there was an almost complete absence of CRFR2 within cancerous tissues, specifically in microvessels and epithelial cells. Additionally, nuclear translocation of UCN1 was observed in cancerous tissue samples. These findings indicate the potential involvement of CRFR2 and UCN1 in the pathophysiology of RCC.

The same principal investigator later explored the relationship between CRFBP and RCC (63). In 78 patient samples, he compared the expression of the CRFBP gene and peptide between cancerous and normal kidney areas. CRFBP mRNA was significantly reduced in cancerous tissues compared to normal tissues. During immunofluorescence, the CRFBP peptide was not identified in ccRCC areas. Correlation analysis revealed that reduced CRFBP mRNA expression was positively associated with the stage and local extension of the disease and the presence of metastases (63). Finally, a recent study on 106 RCC patient samples investigated the presence of UCN3 (64). Researchers observed that UCN3 mRNA was significantly reduced in almost all cancerous tissue samples. Similar findings were demonstrated through western blot and immunohistochemistry tests. Correlation analysis did not reveal any clinicopathological parameter associated with UCN3 expression (64). The results of the above studies indicate that the CRF system may be involved in the carcinogenesis of RCC. Table IV presents a synthesis of the studies on CRF and the kidney mentioned above.

7. Future directions and research needs

Investigations into the function of CRF within the male reproductive system, particularly in the testes, have yielded

Table IV. Summary of the main findings and effects of CRF family members in the kidney.

First author, year	Tissue specimen or cell lines	CRF family member	Findings	Possible mechanism or relation	(Refs.)
Kageyama *et al*, 1999	Kidneys of male rats	UCN1	Low mRNA expression	Initial identification	(58)
Chen *et al*, 2004	Kidneys of male mice	UCN2	Weak expression, no alteration after corticosteroid administration	Identification	(59)
Takahashi *et al*, 2004	Human kidney tissue	UCN3	Expression in distal tubules, mRNA confirmed	Possible autocrine or paracrine role	(61)
Tezval *et al*, 2009	Nephrectomy samples from ccRCC patients	UCN1, CRFR2	Expression in normal and cancerous samples, absence in cancerous microvessels	Potential involvement in RCC pathophysiology	(62)
Tezval *et al*, 2013	Nephrectomy samples from RCC patients	CRFBP	Reduced mRNA in cancerous tissues, absence of peptide in ccRCC	Positive association with disease stage, local extension, and metastases	(63)
Faraj Tabrizi *et al*, 2020	Nephrectomy samples from RCC patients	UCN3	Reduced mRNA in cancerous tissues	No clinicopathological parameter association	(64)

CRF, corticotropin-releasing factor; UCN1, urocortin 1; UCN2, urocortin 2; UCN3, urocortin 3; CRFR2, corticotropin-releasing factor receptor 2; CRFBP, corticotropin-releasing factor-binding protein; ccRCC, clear cell renal cell carcinoma; RCC, renal cell carcinoma.

intriguing but inconsistent results. To elucidate these discrepancies and enhance understanding of the associated mechanisms, targeted studies utilizing human models are essential. These investigations should focus on elucidating the relationship between CRF receptors and the functioning of Leydig cells, testicular processes, and spermatogenesis, which are regulated by specific pathways controlling androgen synthesis. The association between CRFs and CRF-related peptides with urinary malignancies and other diseases deserves more attention. Progress in building sophisticated *in vivo* and *in vitro* models will significantly help researchers reproduce physiological and pathological conditions for structured investigation of the mechanisms in the CRF family. Conditions like IC, which significantly diminish the quality of life and lack effective treatments, underscore the urgent need to reevaluate disease pathways and drive the development of novel therapies. This progress could greatly improve our understanding of the complex functions of CRF in male urogenital organs and facilitate the identification of novel therapeutic strategies. A deeper understanding of CRF's role in these disorders could catalyze therapeutic advancements. Future research should emphasize interdisciplinary approaches to clarify the intricacies of CRF and the potential application of findings for substantial progress in medicine.

8. Conclusions

Members of the CRF family have shown substantial involvement in various physiological and pathological processes, including endocrine regulation within the hypothalamic-pituitary-adrenal axis and intricate local interactions within the urogenital system. CRF is essential in regulating androgen synthesis and influencing Leydig cell functionality within the testes, potentially affecting both normal and impaired reproductive processes. Similarly, its presence in the prostate and its differential effects through CRFR1 and CRFR2 highlight its complex involvement in prostate health and disease, including PCa and BPH. CRF members may modulate urination mechanisms and bladder sensitivity, suggesting a potential role in dysfunctions such as IC. Finally, emerging evidence indicates that the CRF system may be implicated in renal carcinogenesis, though further studies are required to clarify its exact contributions. These findings underscore the need for in-depth investigation of CRF signaling pathways and receptor interactions across different tissues. A comprehensive understanding of these mechanisms is essential for the development of novel, targeted therapies, which may lead to new approaches for treating urogenital disorders, including urinary incontinence, IC, BPH, and urogenital malignancies. Future research must focus on human-based studies and sophisticated modelling techniques to precisely delineate the effects of CRF on the urogenital system and its therapeutic implications.

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Authors' contributions

CMav and CMam conceptualized the project. CMav, EP, AT and CMam contributed to data acquisition, analysis and interpretation. CMav wrote the original draft. AT, EP, CMav and CMam reviewed, edited and wrote the final draft. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, Grammarly and QuillBot were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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